Clinical Ophthalmology

Dovepress
open access to scientific and medical research

Open Access Full Text Article

CLINICAL TRIAL REPORT

Topical Anti-TNFα Agent Licaminlimab (OCS-02) Relieves Persistent Ocular Discomfort in Severe Dry Eye Disease: A Randomized Phase II Study

Lee Shettle[1], Eugene McLaurin[2], Joseph Martel[3], John W Seaman III[4], Georges Weissgerber[5]

[1]Shettle Eye Research, Inc, Largo, FL, USA; [2]Total Eye Care, Memphis, TN, USA; [3]Research Center, Martel Eye Medical Group, Rancho Cordova, CA, USA; [4]Novartis Pharmaceuticals Corporation, Fort Worth, TX, USA; [5]Novartis Institutes for Biological Research, Basel, Switzerland

Correspondence: Lee Shettle, Shettle Eye Research, Inc, Largo, FL, USA, Tel +1 727-674-2500, Fax +1 727-674-2550, Email lshettle@yahoo.com; Eugene McLaurin, Total Eye Care, Memphis, TN, USA, Tel +1-912-441-2128, Email emclaurin6@aol.com

Purpose: To assess the efficacy, safety, and pharmacokinetics of new topical ocular anti-TNFα antibody fragment licaminlimab in the relief of persistent ocular discomfort in severe dry eye disease (DED).

Patients and Methods: Patients with ≥6-month history of DED, regular use of artificial tears, and best-corrected visual acuity (BCVA) of ≥55 letters in each eye (Early Treatment Diabetic Retinopathy Score) at baseline were included in this multicenter, randomized, vehicle-controlled, double masked study. A total of 514 patients were screened. After a 2-week run-in with Vehicle, all qualifying patients received Vehicle eye drops for 4 weeks. Patients with global ocular discomfort score ≥50 at the end of this 4-week period were randomized to receive licaminlimab (60 mg/mL ophthalmic solution) (69 patients) or Vehicle (65 patients) for 6 weeks. The primary efficacy endpoint was change from baseline in global ocular discomfort score at Day 29. Safety assessments included adverse events and ophthalmology examination including intraocular pressure (IOP). Serum licaminlimab levels were also determined.

Results: Change from baseline to Day 29 in global ocular discomfort score was statistically significantly greater for licaminlimab than for Vehicle ($p = 0.041$). No safety issues were identified. Serum licaminlimab was undetectable in most patients; the maximum concentration observed was 8.47 ng/mL.

Conclusion: Topical ocular licaminlimab demonstrated statistically significant improvement in global ocular discomfort score compared to Vehicle in patients with severe DED, with good tolerability, no increase in IOP, and minimal systemic drug exposure.

Keywords: anti-tumor necrosis factor α, dry eye disease, single-chain antibody fragment, topical treatment

Introduction

The overall prevalence of dry eye disease (DED) is approximately 0.5% in the USA increasing with age to 4.4–7.8% among those 50 years and older, constituting 4.9 million US citizens.[1,2] Dry eye is a multifactorial disease characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles.[3] The etiology of DED can involve several deficiencies of the tear film, including the aqueous layer, lipid layer, mucin layer, or a combination of the three. Affected individuals may experience burning sensations, a feeling of eye fatigue, and other symptoms of ocular discomfort, of varying severity, with a significant impact on quality of life. Vision may be substantially impaired in severe cases.

Chronic dryness of the ocular surface is hypothesized to result in nervous stimulation leading to neurogenic inflammation, activation of T-cells, and subsequent release of inflammatory cytokines into the lacrimal glands, tear film, and conjunctiva.[4] Levels of inflammatory cytokines, including tumor necrosis factor α (TNFα), are consistently elevated in tear film.[5] In DED patients, local levels of TNFα in tears or conjunctival tissue have been shown to correlate with disease severity.[6] In animal models of DED, local inhibition of TNFα leads to significant improvement of tear film stability and corneal staining.[7]

Received: 30 March 2022
Accepted: 22 June 2022
Published: 6 July 2022

The majority of DED patients try to manage the disease with artificial tears, but patients with moderate-to-severe discomfort caused by ocular surface inflammation tend not to respond sufficiently to wetting agents only. These agents are not disease modifying, and therefore treatment of this segment of the dry eye disease population represents a clear unmet need. Current therapies for moderate-to-severe DED beyond artificial tears are limited. The main approved treatments include topical ophthalmic preparations of cyclosporine. Cyclosporine ophthalmic emulsion 0.05% (Restasis®) is approved in the USA and Canada only for increasing tear production, not for reducing DED symptoms. It is effective in a minority of patients, but it has a slow onset of action (6 months), and is associated with ocular burning and stinging.[8] Cyclosporine ophthalmic solution 0.09% (Cequa™) is approved in the USA. The response rate in clinical trials was low (although significantly higher than with placebo), and pain on instillation of drops was a common adverse event.[9] Lifitegrast ophthalmic suspension (Xiidra®), currently approved in the USA, Canada and Australia, is an inhibitor of lymphocyte function-associated antigen 1 binding to intercellular adhesion molecule 1, resulting in down-regulation of T-cell-mediated inflammation.[10] It seems to have a quicker onset of action (2–3 weeks) but is associated with local site irritation, dysgeusia and reduced visual acuity. Other approved treatments include a cyclosporine cationic emulsion (Ikervis®) in Europe, and diquafosol solution (Diquas®) and rebamipide suspension (Mucosta®) in Asia.[10] Topical steroids are often used off-label initially along with one of these medications to treat DED but are contraindicated for long-term use due to the risk of cataracts and increased intraocular pressure as side effects.

Systemically applied TNFα inhibitors are effective in several systemic immune-mediated inflammatory disorders but are associated with a number of well-documented safety issues, such as increased risk of infection, malignancy, cardiovascular disease and demyelinating disease. As many ocular inflammatory diseases, such as DED, are characterized by a local, TNFα-driven inflammatory process, the use of systemic TNFα-suppressive therapy is not justified in the treatment of these conditions.[11–14]

Licaminlimab (Oculis SA, Lausanne, Switzerland), formerly known as OCS-02, LME636 and ESBA1622, is a single-chain antibody fragment (scFv) that binds to and neutralizes the activity of human TNFα. Unlike full-length monoclonal antibodies, scFv fragments can penetrate ocular surface tissues when used as eye drops,[15,16] due to the smaller size of the molecule (molecular mass 26.7 kDa as compared with approximately 150 kDa for a full monoclonal antibody).

The aim of the current study is to assess the efficacy, safety, and local tolerability of topical ocular licaminlimab compared with Vehicle for the relief of ocular discomfort associated with severe DED. In addition, the serum concentrations and immunogenicity of licaminlimab following topical ocular administration are described.

Materials and Methods

Study Oversight

Thirty-two investigational sites in the USA participated in this study, 31 sites screened patients, and 26 sites randomized patients. For each participating site, a central institutional review board, Quorum Review IRB, Seattle, Washington, reviewed and approved the clinical study protocol, informed consent form, and all other appropriate study-related documents. The study was designed and performed in accordance with the International Conference on Harmonisation (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice and with the ethical principles of the Declaration of Helsinki. Patients were required to understand and sign the informed consent form. The study is registered with ClinicalTrials.gov (NCT02365519).

Study Design

The study design is summarized in Figure 1. The identification phase was used to detect patients who had persistent, frequent, and severe ocular discomfort despite the use of artificial tears. Eligible patients with severe DED were asked to use artificial tears or equivalent lubricants as needed in the same way as before trial entry for 2 weeks. Only patients who had a global ocular discomfort score ≥60 at the end of the identification phase and were compliant with study recording procedures continued into the treatment phase.

In order to further enrich the study population by ensuring that patients who responded to vehicle did not continue in the study, on entry to the 10-week treatment phase, patients were told that they were randomized to active treatment or Vehicle

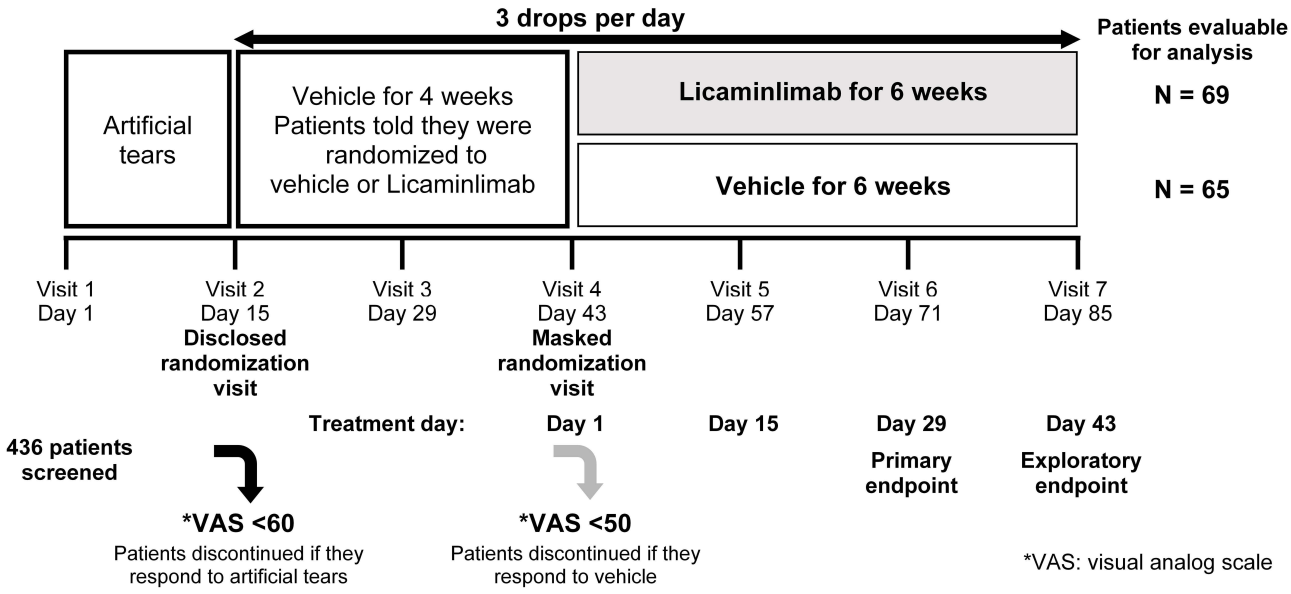

Figure 1 Study design.

(without any actual randomization taking place) in a 1:1 ratio. This was termed the disclosed randomization visit, although the assigned treatment was masked to patients and investigators. All patients then received Vehicle eye drops for 4 weeks. Patients with a global ocular discomfort score <50 at the end of this 4-week period were discontinued. The remaining patients in the study were then randomized to receive either licaminlimab or Vehicle for 6 weeks (the start of this treatment period was masked to investigators, patients, and sponsor monitors, and was referred to as the masked randomization visit). During the treatment period, licaminlimab 60 mg/mL ophthalmic solution or Vehicle was administered topically as one drop to each eye three times per day. Throughout the study, patients recorded daily dosing of, as relevant, artificial tears and their study medication in a patient diary. Diaries were reviewed by site personnel and Sponsor monitors for compliance.

Randomization was performed by the Sponsor using a validated system that generated randomization numbers and automated the random assignment of treatment arms to randomization numbers in the specified ratio.

Study Population

Patient eligibility criteria included age ≥18 years, physician diagnosis of DED of at least 6 months prior to Visit 1; use of artificial tears, gels, lubricants or rewetting drops on a regular basis; best-corrected visual acuity (BCVA) of 55 letters or greater in each eye as measured by Early Treatment Diabetic Retinopathy Score (ETDRS; letters read method) at Visit 1; hyperemia: a score of at least 1 (according to the McMonnies redness photographic redness scale) in at least two of four quadrants (inferior, superior, nasal, temporal) at Visit 1.

Key exclusion criteria included the following: patients were excluded if they were contact lens users; if they had any acute infection or non-infectious ocular condition of the anterior or posterior segments within 1 month of study entry; had any corneal surgery including keratorefractive surgeries or any intraocular surgery including cataract surgery within 6 months of Visit 1, had any chronic ocular degenerative condition that, in the opinion of the Investigator, could have advanced during the study; used nasal, inhaled, systemic or topical corticosteroids within 1 month of study entry; had any medical condition (systemic or ophthalmic) that may have, in the opinion of the Investigator, precluded safe participation in the study.

Assessments

Efficacy assessments included change from baseline in global ocular discomfort score and percentage of patients with improvement in global ocular discomfort score >20. Exploratory assessments included change from baseline in signs of DED. These included physician graded conjunctival hyperemia, grading using the 6-point McMonnies redness scale; fluorescein corneal staining score based on the degree of staining across five regions (central, superior, temporal, nasal,

inferior) in each eye after application of a sterile sodium fluorescein strip, with a maximum score of 20 per eye; Meibomian gland assessment rating inflammation of the lid margin (thickening, vascularity, telangiectasia) and character of secretion (quality, expressibility, volume) to provide a composite score; tear film osmolarity determined using the TearLab™ system (TearLab Corporation, Escondido, CA). Assessment of topical effect of OS-02 was measured as change from baseline in momentary ocular discomfort. Safety assessments included extent of exposure to licaminlimab, complete ophthalmic examination (slit-lamp, dilated fundus examination, BCVA, IOP measurement), and collection of adverse events (AEs).

Study End Points

The primary efficacy endpoint was change from baseline in global ocular discomfort score at treatment day 29. Global discomfort score was a composite of discomfort frequency and severity, based on the Symptom Assessment iN Dry Eye (SANDE) questionnaire. The SANDE questionnaire gives a reliable measure of DED symptoms using a 100 mm horizontal linear visual analogue scale.[17] These data were recorded on an electronic subject reported outcome device, which only allows a given time window each day for recording of the symptoms (forced daily recording).

The secondary efficacy endpoint was the percentage of patients with improvement in global ocular discomfort score >20 from baseline to treatment day 29.

Statistical Analyses

Analysis of the primary efficacy endpoint, change from baseline to treatment day 29 in global ocular discomfort score, was based upon a mixed model repeated measures analysis with terms for baseline global discomfort score, treatment day, treatment, and treatment day by treatment interaction. Multiple covariance structures were considered, with the best fitting structure selected based upon Akaike Information Criterion. Estimates of differences, 90% confidence intervals, and p-values were provided. The analysis of the secondary efficacy endpoint, percentage of patients with improvement in global ocular discomfort score >20 from baseline to treatment day 29, was based upon a chi-square test. Estimates of the difference, 90% Wald confidence interval, and p-values were provided. Exploratory variables were summarized with descriptive statistics by treatment group. Analysis of the primary safety endpoints were summarized with descriptive statistics by treatment group. The primary analysis set for primary and secondary efficacy endpoints was the per protocol analysis set, which was a subset of the full analysis set and excluded all patients who had met any of the critical deviation criteria identified in the Deviations and Evaluability Plan. The primary analysis set for exploratory efficacy endpoints was the full analysis set, which included all randomized patients with at least a post-baseline primary endpoint assessment. Safety endpoints were summarized under the safety analysis set, which included all patients exposed to study treatment following randomization.

Results

Patient Disposition

Patient disposition is summarized in Figure 2. The study was conducted between March 9 and October 16, 2015. Five hundred and fourteen patients were screened, and 134 were randomized (masked randomization). Most patients (approximately 98%) completed the treatment phase of the study in each treatment arm, although three patients discontinued either due to an AE or withdrawal from the study.

All randomized patients with at least one post-baseline primary endpoint assessment were included in the full analysis set and all treated patients were included in the safety set. The per protocol set was a subset of randomized patients excluding those with critical protocol deviations. Three patients were excluded from the per protocol set: two patients in the licaminlimab arm (both due to use of forbidden concomitant medication) and one in the Vehicle arm (due to diagnosis of DED <6 months prior to study entry).

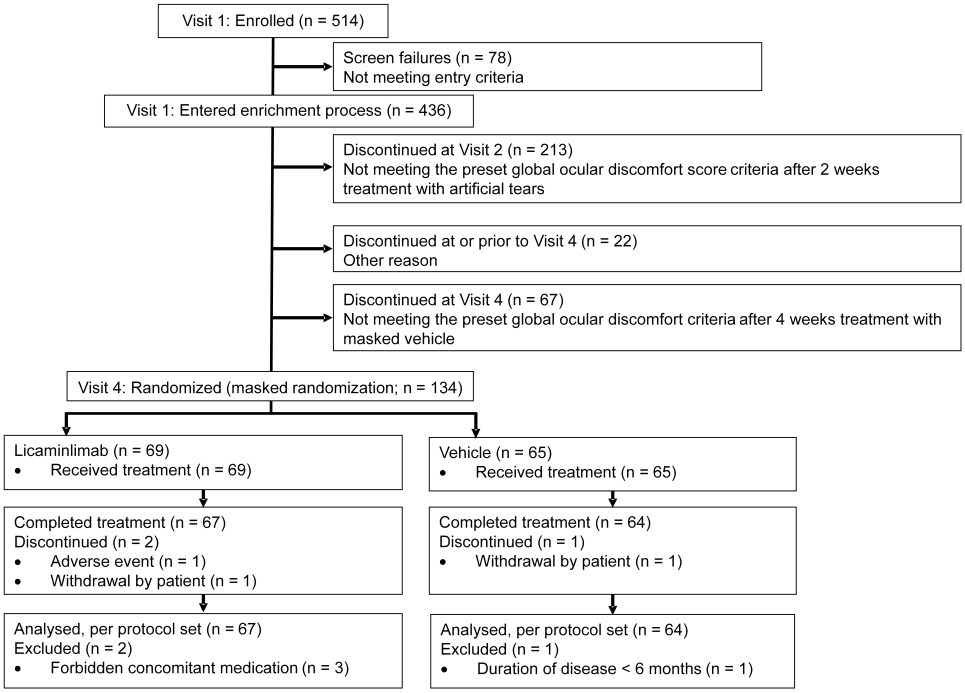

Figure 2 Disposition of patients.

Baseline Demographics and Clinical Characteristics

Patients had a mean age of approximately 60 years and were most commonly female and Caucasian. There were no notable differences between treatment arms in demographic characteristics (Table 1). Baseline ocular discomfort scores were similar in the two arms (for the Per Protocol analysis set, mean ± SD was 77.9 ± 13.89 in the licaminlimab arm and 80.3 ± 12.56 in the vehicle arm).

Efficacy Outcomes

Primary efficacy outcomes are shown for the per protocol set in Table 2. The change from baseline to treatment day 29 in global ocular discomfort score was significantly greater for licaminlimab (–7.9) than for Vehicle (–3.6) (90% CI –7.7, –0.8; p = 0.041) (Figure 3).

Secondary efficacy outcomes, the percentage of patients with improvement in global ocular discomfort score >20 from baseline (treatment day 1) to treatment day 29, are presented for the per protocol set in Table 3. The percentage of patients with more than a 20 units improvement in global ocular discomfort score was greater for licaminlimab (17.9%) compared to Vehicle (4.7%), (90% CI on difference 4.4, 22.1; p-value = 0.018) (Table 3). Results of exploratory endpoints (physician graded conjunctival hyperemia, corneal staining, Meibomian gland assessment, and tear film osmolarity) were similar across treatment groups (Table 4).

Safety Outcomes

The serum concentrations of total licaminlimab were low, ranging from Below the Limit of Quantitation (<0.250 ng/mL) to 8.47 ng/mL. Licaminlimab was not detectable in the majority of patients. On treatment day 15, 29, and 43, the percentage of patients in which licaminlimab was not detectable was 82.1%, 71.9%, and 67.9%, respectively.

Anti-licaminlimab antibodies were detected in 26.9–34.9% of the patients prior to the start of the OSC-02 dosing phase. In the Vehicle group, the incidence of antidrug antibodies did not change markedly during the study, ranging from 37.7% to 41.7%. In contrast, the incidence of antidrug antibodies in the OSC-02 group increased after the administration of the first dose with the incidence increasing with increased duration of dosing. The incidence of antibodies was 45.6%,

Table 1 Baseline Demographic Characteristics (Randomized Set)

	Licaminlimab (N = 69) n (%)	Vehicle (N = 65) n (%)
Age (years)		
n	69	65
Mean (SD)	61.7 (13.05)	58.8 (14.48)
Median (range)	60 (24–90)	61 (22–86)
Age group, n (%)		
<65	44 (63.8)	42 (64.6)
≥65	25 (36.2)	23 (35.4)
≥65 to <75	10 (14.5)	14 (21.5)
≥75 to <85	14 (20.3)	8 (12.3)
≥85 to <95	1 (1.4)	1 (1.5)
Sex, n (%)		
Male	8 (11.6)	11 (16.9)
Female	61 (88.4)	54 (83.1)
Race, n (%)		
White	51 (73.9)	52 (80.0)
Black or African American	9 (13.0)	7 (10.8)
Asian	8 (11.6)	4 (6.2)
Native Hawaiian or other Pacific Islander	1 (1.4)	0 (0.0)
Other	0 (0.0)	2 (3.1)

Abbreviations: N, number of patients in treatment group; n, number of patients with data at visit; SD, standard deviation.

Table 2 Analysis of Change from Baseline in Global Ocular Discomfort Score at Treatment Day 29 (Per Protocol Set)

	Licaminlimab (N = 67)	Vehicle (N = 64)
Baseline		
n	67	64
Mean (SD)	77.9 (13.89)	80.3 (12.56)
Treatment day 29		
n	64	60
Mean (SD)	71.4 (20.61)	75.9 (15.00)
Change from baseline[a]		
Mean (SE)	–7.9 (1.45)	–3.6 (1.49)
90% CI	(–10.3, –5.5)	(–6.1, –1.2)
Difference in change from baseline[b]		
Mean (SE)	–4.3 (2.08)	
90% CI	(–7.7, –0.8)	
p-value	0.041	

Notes: [a]Based on mixed model with terms for baseline, treatment day, treatment, and treatment day by treatment interaction. [b]Difference = licaminlimab – Vehicle.
Abbreviations: CI, confidence interval; N, number of patients in treatment group; n, number of patients with data at visit; SD, standard deviation; SE, standard error.

79.3%, and 86.8% on treatment day 15, treatment day 29, and treatment day 43, respectively. The titers ranged from 1.26 to 3330, 1.39 to 4180, and 2.89 to 29,400, respectively.

Treatment-emergent AEs (TEAEs) were reported in 13/69 (18.8%) of the licaminlimab group and 9/65 (13.8%) of the Vehicle group. The most common AEs in the licaminlimab group were dry eye and eye pruritus, each of which were reported

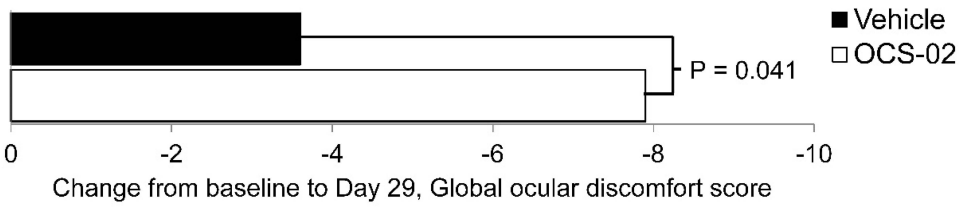

Figure 3 Change from baseline to day 29 in global ocular discomfort score, (per protocol set).

in 2 (2.9%) patients but did not occur in the Vehicle group (Table 5). No other specific TEAEs occurred in more than one patient per treatment group. Two patients in each treatment group had TEAEs assessed as related to an investigational product. One patient in the Vehicle group had a serious adverse event (pneumonia) and one patient in the licaminlimab group discontinued treatment due to TEAEs (conjunctivitis), although the events were not treatment-related.

Mean changes from baseline in IOP by treatment group were minimal (–0.3 mmHg for licaminlimab and +0.2 mmHg for Vehicle at treatment day 43) and similar in all study arms. No discernable trend toward a decrease in BCVA was

Table 3 Analysis of Percentage of Patients with More Than 20 Units Improvement in Global Ocular Discomfort Score from Baseline at Day 29 (Per Protocol Set)

	Licaminlimab (N = 67)	**Vehicle (N = 64)**
n (%) SE	12 (17.9) 4.7	3 (4.7) 2.6
Difference (SE)[a] 90% CI [b] p-value [b]	13.2 (5.4) (4.4, 22.1) 0.018	

Notes: [a]Difference = licaminlimab – Vehicle. [b]Based on chi-square test and Wald interval.
Abbreviations: N, number of patients in treatment group; n, number of patients with improvement; SE, standard error.

Table 4 Descriptive Statistics for Exploratory Efficacy Parameters (Full Analysis Set)

Parameter	**Licaminlimab**	**Vehicle**
Physician graded conjunctival hyperemia (sum score)		
Treatment day −14 mean (SD)	4.8 (2.43)	4.5 (2.26)
Treatment day 29 mean (SD)	4.1 (2.42)	3.9 (2.28)
Change from baseline[a] mean (SD)	−0.7 (2.21)	−0.6 (2.24)
Corneal staining (sum score)		
Treatment day −28 mean (SD)	5.6 (2.66)	6.2 (3.08)
Treatment day 29 mean (SD)	4.4 (2.37)	4.6 (2.82)
Change from baseline[b] mean (SD)	−1.1 (2.32)	−1.4 (2.54)
Meibomian gland assessment (sum score)		
Treatment day −28 mean (SD)	9.4 (4.37)	9.7 (4.43)
Treatment day 29 mean (SD)	9.4 (4.45)	9.0 (4.56)
Change from baseline[b] mean (SD)	0.0 (3.15)	−0.7 (3.65)
Tear film osmolarity		
Treatment day −14 mean (SD)	301.5 (13.04)	306.7 (16.38)
Treatment day 29 mean (SD)	304.1 (14.57)	303.4 (14.75)
Change from baseline[a] mean (SD)	0.8 (19.68)	−3.5 (20.71)

Notes: [a]Baseline = treatment day −14, [b]Baseline = treatment day −28.

Table 5 Summary of Treatment Emergent Adverse Events (Safety Analysis Set)

	Licaminlimab (N = 69)			Vehicle (N = 65)		
	n	%	E	n	%	E
Patients with at least one TEAE	13	(18.8)	24	9	(13.8)	17
Related to study treatment	2	(2.9)	3	2	(3.1)	2
Patients with any serious TEAE	0	(0.0)	0	1	(1.5)	1
Deaths	0	(0.0)	0	0	(0.0)	0
Nonfatal serious TEAE	0	(0.0)	0	1	(1.5)	1
Related to study treatment	0	(0.0)	0	0	(0.0)	0
Patients with TEAE leading to study discontinuation	1	(1.4)	2	0	(0.0)	0
Related to study treatment	0	(0.0)	0	0	(0.0)	0
TEAE ≥2%						
Dry eye	2	(2.9)	4	0	(0.0)	0
Eye pruritus	2	(2.9)	3	0	(0.0)	0
Adverse drug reactions ≥1%						
Cough	0	(0.0)	0	1	(1.5)	1
Dysgeusia	0	(0.0)	0	1	(1.5)	1
Eye pruritus	1	(1.4)	1	0	(0.0)	0
Lacrimation increased	1	(1.4)	2	0	(0.0)	0

Notes: If a patient has multiple occurrences of an AE, the patient is presented only once in the respective patient count column (n) for the corresponding AE. Events are counted each time in the event (E) column. Adverse drug reactions were defined as AEs assessed as treatment-related by the investigators. Adverse events are coded using MedDRA version 17.0.
Abbreviations: AE, adverse event; E, number of events; MedDRA, Medical Dictionary for Regulatory Activities; N, total number of patients in each treatment group; n, number of patients with the events; TEAE, treatment-emergent adverse event.

observed in either treatment group. There were no meaningful changes in any fundus parameter or slit-lamp parameter over the course of the clinical trial.

Discussion

DED prevalence is high in adults and increases with age.[1,2] Ocular lubricants/artificial tears are frequently used to manage DED, but do not treat the underlying causes of the condition and for a large proportion of patients do not resolve symptoms of severe ocular discomfort. For these patients, treatment options are very limited. Historically, demonstrating effects on both signs and symptoms of DED in clinical studies has been challenging, even in large Phase III programs.[10] Therefore, for this single Phase II study, the primary endpoint was chosen as the relief of ocular discomfort, which is considered the highest unmet medical need in severe DED. Objective signs were included only as exploratory endpoints. Inclusion criteria for the study therefore also focused primarily on ocular discomfort rather than objective signs, for example corneal staining.

During the identification phase of this study, patients with severe DED were asked to use artificial tears or equivalent lubricants as needed. The purpose of this phase was to identify patients who had persistent, frequent, and severe ocular discomfort despite the use of artificial tears. This resulted in a relatively high rate of screening failures. While this may affect extrapolation of results to the general population of patients with dry eye disease, it did enable the study specifically to recruit patients with severe ocular discomfort, as intended.

The topical ocular TNFα inhibitor licaminlimab showed efficacy in the treatment of this population of patients with severe DED and was statistically significantly more effective than Vehicle in reducing ocular discomfort. Secondary efficacy endpoints also indicated that licaminlimab eye drops were effective. The percentage of patients with an improvement in global ocular discomfort score >20 from baseline to treatment day 29 was greater for licaminlimab compared to Vehicle.

Licaminlimab appeared to be well tolerated in this study, with no major safety differences between licaminlimab and Vehicle treatment groups. The good tolerability of licaminlimab allowed masking to be maintained well in the study, which might not have been the case with an active treatment that was associated with ocular irritation. The most common AEs in the licaminlimab group were dry eye and eye pruritus (both less than 3% of patients). Complete ophthalmic examinations including slit-lamp, dilated fundus examination, BCVA, and IOP, revealed no safety issues or differences between treatment arms.

Assessment of licaminlimab serum levels following topical ocular application showed that systemic exposure was minimal. The majority of patients did not have detectable serum concentrations of licaminlimab, and the maximum concentration observed was 8.47 ng/mL. The anti-TNFα antibodies currently in clinical use are administered subcutaneously or intravenously, and typically achieve serum concentrations in the μg/mL range.[11–14] The low serum levels observed following topical ocular application of licaminlimab could allow treatment of ocular conditions without the class effect risks associated with current systemic anti-TNFα agents.

Anti-licaminlimab antibodies were observed pre-treatment in similar proportions of the licaminlimab and Vehicle groups prior to administration of the first dose of licaminlimab. In the licaminlimab group, the incidence of antibodies increased after starting treatment and with duration of dosing, while there was little change seen in the Vehicle group. Anti-licaminlimab antibodies, either pre-existing or treatment emergent, did not appear to have any effect on serum concentrations of licaminlimab, efficacy parameters or adverse events. The presence of pre-existing antibodies in human serum believed to arise as a consequence of proteolysis of endogenous immunoglobulins and not indicative of prior treatment with a therapeutic antibody, has been noted for several systemically administered novel antibody formats, and in some patient populations may be associated with a higher risk of development of post-treatment antidrug antibodies (ADA).[18] Antidrug antibody development has been commonly observed in patients treated with systemic anti-TNFα agents and has been associated with decreased therapeutic responses in some patients.[19] However, the development of ADA in the treatment of ocular disease with topical or even intravitreal therapies has been little studied, for example, none of the five studies included in a recent review on intravitreal administration of anti-TNFα agents to treat uveitis assessed ADA.[20] The relevance to therapeutic outcomes of systemic ADA following topical licaminlimab treatment therefore remains unknown, although in this study no obvious effects were apparent.

Limitations of this study included its short duration, which did not permit assessment of longer term safety or therapeutic effects of licaminlimab. Also, because of the focus in this study on ocular discomfort, objective signs of DED, including physician graded conjunctival hyperemia, fluorescein corneal staining, meibomian gland assessment, and tear film osmolarity were included only as exploratory endpoints with no statistical comparisons. Such objective signs of DED could be assessed further in future studies.

Conclusion

This study with topical ocular licaminlimab showed improved efficacy in the relief of ocular discomfort in patients with severe DED despite the use of artificial tears, with no obvious systemic safety issues. Topical ocular licaminlimab appears to be safe and well tolerated in this study, with no effect on IOP or other ophthalmic parameters, along with minimal systemic exposure. Although the optimal dose regimen remains to be determined, the results of this study suggest that licaminlimab could provide an effective ophthalmic treatment for persistent ocular discomfort due to severe DED, without the class-effect risks of systemic TNFα blockade.

Data Sharing Statement

Datasets generated during this study are not currently available for sharing.

Acknowledgments

The authors would like to thank Anna Martin (an employee of Alcon Research Ltd) for her work in the coordination and conduct of the study, and Karen Welfare and Phil Hunt (both of Southdown Medical Writing Ltd, UK, funded by Oculis SA) for their writing assistance in drafting the manuscript. The design and conduct of this study were funded by Novartis/Alcon, the sponsor at the time the trial was conducted. The preparation of this manuscript was funded by Oculis SA, who acquired licaminlimab (formerly LME636) from Novartis/Alcon after completion of the study.

Disclosure

J.W.S III and G.W were employees and equity holders of Alcon/Novartis at the time the study was conducted. L.S, J.M, and E.M received financial and non-financial support (grants) from Alcon Research Ltd for the conduct of the study. Outside of the reported study, L.S reports financial support from the following clinical research sponsors; Aerie Pharmaceuticals, Allysta Pharmaceutical Inc., Bausch & Lomb, Hovione Scientia Ltd, Kala Pharmaceuticals Inc., Novartis, Ocugen, Inc., Ocular Technologies Sarl, Ocular Therapeutix Inc., OmegaD LLC, Osmotica Pharmaceutical Corp., Santen Inc, Senju Pharmaceutical Co., Silk Technologies Ltd, Valeant Pharmaceuticals. Outside of the reported study, E.M reports financial support (grants) from the following; Aldeyra, Aurinia, Axero Vision, HanAll, Kowa, Mitotech, ReGenTree, Topivert. The authors report no other conflicts of interest in this work.

References

1. Pflugfelder SC. Prevalence, burden, and pharmacoeconomics of dry eye disease. *Am J Manag Care*. 2008;14(3 Suppl):S102–S106.
2. Schaumberg DA, Dana R, Buring JE, Sullivan DA. Prevalence of dry eye disease among US men: estimates from the physicians' health studies. *Arch Ophthalmol*. 2009;127:763–768. doi:10.1001/archophthalmol.2009.103
3. Craig JP, Nichols KK, Akpek EK, et al. TFOS DEWS II definition and classification report. *Ocul Surf*. 2017;15(3):276–283. doi:10.1016/j.jtos.2017.05.008
4. Baudouin C. The pathology of dry eye. *Surv Ophthalmol*. 2001;45(2 Suppl):S211–S220. doi:10.1016/s0039-6257(00)00200-9
5. Lee SY, Han SJ, Nam SM, et al. Analysis of tear cytokines and clinical correlations in Sjögren syndrome dry eye patients and non-Sjögren syndrome dry eye patients. *Am J Ophthalmol*. 2013;156:247–253. doi:10.1016/j.ajo.2013.04.003
6. Massingale ML, Li X, Vallabhajosyula M, Chen D, Wei Y, Asbell PA. Analysis of inflammatory cytokines in the tears of dry eye patients. *Cornea*. 2009;28(9):1023–1027. doi:10.1097/ICO.0b013e3181a16578
7. Trousdale MD, Zhu Z, Stevenson D, Schechter JE, Ritter T, Mircheff AK. Expression of TNF inhibitor gene in the lacrimal gland promotes recovery of tear production and tear stability and reduced immunopathology in rabbits with induced autoimmune dacryoadenitis. *J Autoimmune Dis*. 2005;2:6. doi:10.1186/1740-2557-2-6
8. Restasis® (cyclosporine ophthalmic emulsion 0.05%) [prescribing information]. Irvine, CA: Allergan, Inc; 2012.
9. Cequa™ (cyclosporine ophthalmic solution) 0.09% [prescribing information]. Cranbury, NJ: Sun Pharmaceutical Industries, Inc; 2018.
10. Holland EJ, Darvish M, Nichols KK, Jones L, Karpecki PM. Efficacy of topical ophthalmic drugs in the treatment of dry eye disease: a systematic literature review. *Ocul Surf*. 2019;17(3):412–423. doi:10.1016/j.jtos.2019.02.012
11. Humira® (Adalimumab) [prescribing information]. North Chicago, IL: AbbVie Inc; 2021.
12. Remicade® (infliximab) [prescribing information]. Horsham, PA: Janssen Biotech, Inc; 2013.
13. Cimzia (certolizumab pegol) [prescribing information]. Smyrna, GA: UCB, Inc; 2019.
14. Simponi® (golimumab). [prescribing information] Horsham, PA: Janssen Biotech, Inc; 2018.
15. Brereton HM, Taylor SD, Farrall A, et al. Influence of format on in vitro penetration of antibody fragments through porcine cornea. *Br J Ophthalmol*. 2005;89(9):1205–1209. doi:10.1136/bjo.2005.066225
16. Thiel MA, Coster DJ, Standfield SD, et al. Penetration of engineered antibody fragments into the eye. *Clin Exp Immunol*. 2002;128(1):67–74. doi:10.1046/j.1365-2249.2002.01808.x
17. Amparo F, Schaumberg DA, Dana R. Comparison of two questionnaires for dry eye symptom assessment: the ocular surface disease index and symptom assessment in dry eye. *Ophthalmology*. 2015;122(7):1498–1503. doi:10.1016/j.ophtha.2015.02.037
18. Xue L, Rup B. Evaluation of pre-existing antibody presence as a risk factor for posttreatment anti-drug antibody induction: analysis of human clinical study data for multiple biotherapeutics. *AAPS J*. 2013;15(3):893–896. doi:10.1208/s12248-013-9497-z
19. Atiqi S, Hooijberg F, Loeff FC, Rispens T, Wolbink GJ. Immunogenicity of TNF-inhibitors. *Front Immunol*. 2020;11:312. doi:10.3389/fimmu.2020.00312
20. Leal I, Rodrigues FB, Sousa DC, et al. Efficacy and safety of intravitreal anti-tumour necrosis factor drugs in adults with non-infectious uveitis – a systematic review. *Acta Ophthalmol*. 2018;96:e665–e675. doi:10.1111/aos.13699